REMARKS

Reconsideration and withdrawal of the requirement for restriction are respectfully requested in view of the remarks herein.

I. STATUS OF THE CLAIMS AND FORMAL MATTERS

Claims 1, 4-6 and 8-28 are now pending, with claims 1, 4-6 and 8-25 under examination. Claims 1, 20 and 25 have been amended, and claims 2, 3 and 7 have been canceled, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents.

No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and the originally-filed claims and the claims herewith are and were in full compliance with the requirements of 35 U.S.C. §112. The claims amended herein are not amended for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, the amendments to the claims are presented simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel.

II. BRIEF DISCUSSION OF THE INVENTION

The present invention provides for a novel approach in formulation of peptidic B-cell epitopes or CTL epitopes, against which it is desired to raise an immune response. The inventive solution is the coupling of the (known) B-cell epitopes or CTL epitopes at their N-termini to a polyhydroxypolymer carrier to which is also attached N-terminally coupled (known) T-helper epitopes. Accordingly, the invention is of use when the skilled artisan is facing the task of preparing an immunogen against which he is to raise an immune response. This widespread potential use is what renders the present claims relatively broad - the present technology is

applicable to all peptidic B-cell epitopes or CTL epitopes against which it could be useful to raise an immune response.

III. THE REJECTIONS UNDER 35 U.S.C. §112 ARE OVERCOME

Claims 1-25 were rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly is not enabled for antigenic determinants or epitopes other than an AB fragment (SEQ ID NO:2, residues 673-714), P2 and P30 coupled to an activated polyhydroxypolymer carrier. The rejection is respectfully traversed.

The Office Action states that the claims are drawn very broadly to an immunogen which comprises at least two antigenic determinants, wherein one is at least one B-cell epitope and/or at least one CTL epitope, and wherein the other includes a T helper cell epitope, and wherein both epitopes are coupled to an activated polyhydroxypolymer carrier. Additionally, the Office Action states that "the specification fails to privde any guidance for the successful construction of any immunogen." Applicants respectfully disagree with this assertion and believe that the Office Action has mischaracterized the invention. The present invention is directed towards the coupling of the (known) B-cell epitopes or CTL epitopes at their N-termini to a polyhydroxypolymer carrier to which is also attached N-terminally coupled (known) T-helper epitopes in order to prepare effective immunogens, where it is desired to raise an immune response against a given CTL or B-cell epitope. As the novelty of this invention lies in the N-termini coupling, a process which is widely applicable to make a large variety of immunogens, it does not make any sense to limit the scope of the claims to *e.g.* AS-derived epitopes. These are used solely as examples, but the specification also demonstrates that the technology can be applied when intending to raise an immune response against a hapten derived from the C-terminus of OspC, *see, e.g.*, Example 2.

The traditional method of raising an immune response against a hapten or a weak immunogen has been to couple it to a T-helper epitope containing carrier protein by means of chemical conjugation. A more recent refinement of this technology has consisted of the coupling of the hapten or weak immunogen to shorter, identified T-helper epitopes. In the case where the

hapten is an autologous CTL or B-cell epitope in the host to be immunized, the T-helper epitope needs to be foreign to the host and to the hapten, whereas in the case of foreign antigens, this is not necessarily a requirement, because T-helper epitopes from the same foreign antigen may provide for sufficient T-cell help.

As currently amended herein, claim 1 is now limited to the use of epitopes constituted by amino acid sequences that are separately coupled to a polyhydroxypolymer carrier at their N-termini. The claim as amended hence does not read on any type of epitope, but merely on peptidic epitopes.

Identification of linear B-cell epitopes and of CTL and T-helper epitopes has been done in the past and is continuing today and most antigens of interest are at least partially epitope mapped. Further, computer algorithms do exist to assist in identifying epitopes in proteins. Therefore, the epitope "building blocks" of the present invention are all available to the skilled person. It should also be emphasized, that the precise choice of B-cell epitope or CTL epitope is irrelevant - the invention should be considered an attractive alternative to known carrier conjugate technology which would be routine applied by the skilled artisan desiring to prepare an immunogen based on an isolated B-cell epitope or CTL-epitope.

Further, the present invention demonstrates by using the P2 and P30 T helper epitopes (epitopes that are in no way exceptional or "magic"), that the principle of the present invention works, see, e.g., Example 2 where it is demonstrated that a C-terminal epitope from the OspC polypeptide of Borrelia burgdoferi becomes immunogenic when being part of an immunogen as claimed. The latter also contradicts the Office Action's assertion that only Aβ fragments are enabled - the patent application demonstrates the efficacy of the inventive technology using an immunogen other than Aβ.

The Office Action also states that a person of skill in the art "would recognize that prediciting the efficacy of using an immunogen *in vivo* based solely on the construction and use of a single example is highly problematic." Office Action at 4. However, it is respectfully asserted that the tenor of the cited passage in the MPEP (§2164.02) is that a working example is NOT a requirement. And, in this case a working example has actually been produced (Example

2 is NOT prophetic). Further, the art of immunology is not unpredictable. The Office Action has not in any way divulged why a skilled immunologist should face problems in choosing a combination of e.g. B-cell epitopes and T-helper epitopes in order to prepare an immunogen of the invention.

The Office Action further states that under the Wands factors, the specification is not enabling. Applicants respectfully disagree. The Examiner is respectfully invited to again review *In re Wands*, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988), wherein the Federal Circuit stated at 1404 that:

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... [Citations omitted].

Against this background, determining whether undue experimentation is required to practice a claimed invention turns on weighing the factors summarized in *In re Wands*. These factors include, for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims; all of which must be taken into account.

The Office Action stated on page 5 that "[t]he skilled artisan readily recognizes that protein chemistry is an unpredictable area" and that [p]roteins with deletion, insertion or substitution/replacement of single amino acid residues may lead to both structural and functional

changes in biological activity and immunological recognition (in an epitope)." These statements fail to recognize that linear epitopes are not subject to the problems with conformational characteristics. It has been repeatedly proven that linear epitopes in conformationally unrestricted form are capable of triggering immune responses against the same epitope conformationally restricted in a protein. It is respectfully asserted that there today exist vaccines and immunogens that are prepared from short peptides, and these are by nature relying on the presence of linear epitopes, not on conformational epitopes.

Additionally, the Office Action states that Otvos *et al.* demonstrates that large quantities of experimentation may be necessary even when known T cell epitopes are used in the present invention. Quite simply, Otvos *et al.* is irrelevant to the present invention. It is true that a hybridoma only reacts with one single T-helper epitope in Otvos *et al.*, but two things are of relevance here. First of all, there is no requirement in the presently pending claims that the claimed immunogens should be generally applicable in a broad population: if used to immunize inbred mice with a view to producing monoclonal antibodies, the T-helper epitope merely has to be one which is known to stimulate T-helper cells in that particular mouse strain (see also Example 2, where it is emphasized that the chosen T-helper epitopes match the haplotype of the immunized mice) - and, even if one of the immunogens failing under the definition in claim 1 should only prove to be immunogenic in, say, 1% of an outbred population, it is nevertheless an immunogen in that 1% of the population. Second, the specification clearly points out that if one wishes to prepare a generally applicable immunogen, then a promiscuous T-helper epitope should be used. Hence, the specification provides ample guidance for the skilled person to select the T-helper epitope that suits the relevant need. Briefly, if used for immunization of inbred mice, the T-helper epitope should match the MHC Class II haplotype of the inbred mice; if used for vaccination of a outbred population, the T-helper epitope should be promiscuous, as is described in the specification.

The Office Action also cites to Calvo-Calle *et al.* to show that "antibody titers produced by similar epitopes on their construct vary greatly" and that it would therefore "entail undue experimentation to practice the claims to the full extent due to the unpredictability of the

resultant immune response to any given epitope. Again, the present constructs as claimed are intended to be effective in various populations, be it a specific mouse strain or an entire outbred population, and in this context it is noteworthy that Calvo-Calle *et al.* demonstrates that all constructs used ARE immunogenic in inbred mice, *i.e.* mice having a defined haplotype for recognizing specific T-helper epitopes, which is described as one of the possible uses for the present invention.

Regarding the state of the prior art, the Office Action states that the prior art demonstrates the variety of immune responses that may be stimulated by use of different epitopes. These statements could, in our opinion, be applicable to any conjugation technology, but it does not appear to be a sound argument against enablement of an invention, that problems could be theoretically encountered while using a certain type of technology. The problems that might follow an attempt to scale up from an experimental setup is known in a large number of technologies (purification, fermentation, refolding of proteins, to name but a few). And, even though the Marguerite reference demonstrates some variability in the immunogenicity of various constructs, none of the tested constructs proved to be non-immunogenic. A question of enablement relates to whether the skilled person could prepare and use the presently invented immunogens, not whether he could always prepare and use the invention so as to render it the best solution to solve his current problem.

Furthermore, the Office Action additionally states that Sela *et al.* teaches that two B and T cell epitopes, having essentially identical molecular weight, size, shape and compositions, have significant differences in their immunogenicity, which is likely attributed to their three-dimensional structure. Again, it is respectfully stated that this assertion fails to realize that linear epitopes are not subject to the problems with conformational characteristics. And, this argument would be better suited towards methods of finding or identifiying B or T cell epitopes. In contrast, the present claims require that the epitopes of the presently claimed conjugates ARE recognized as B-cell epitopes and T-helper epitopes, respectively. The typical application of the inventive technology is to take a known B-cell epitope or CTL-epitope and couple it N-terminally to a polyhydroxypolymer carrier and to take a known T-helper epitope and to couple

it to the same polyhydroxypolymer carrier. The present invention is not concerned with identification of epitopes, but with practicalities having to do with induction of immune responses against known epitopes.

Finally, the Office Action states that Goldsby *et al.* teaches that "the development of an immune response does not necessarily mean that a state of protective immunity has been achieved" and that "development of immunological memory is crucial for successful use of an immunogen." Office Action at 7. First, an immunogen need not confer protective immunity in order to be an immunogen - the only requirement is the ability to induce an immune response, for instance, as is the case when immunizing mice to prepare hybridomas. Second, these points address some general issues relating to vaccine technology, which may be highly relevant for the developer of a vaccine, but which are certainly not specific or relevant for the enablement of the present invention. The skilled person would have to consider the points raised in Goldsby when developing any vaccine, not only the vaccines that may utilize the present technology.

In summary, contrary to the assertions in the Office Action, while the breadth of the claims is wide, the quantity of experimentation necessary is low, the amount of direction or guidance presented in the specification is high (one of skill in the art has adequate direction to select and couple the appropriate epitopes, working examples are presented in the specification, the prior art referenced concerns only the selection of epitopes, not the coupling of those epitopes, the relative skill of those in the art is high, and while determination of new epitopes is relatively high in unpredictability, the selection of known epitopes and their conjugation is not unpredictable.

Consequently, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-25 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not sufficiently described to convey to one of skill in the art that applicants had possession of the claimed invention at the time of filing. The rejection is respectfully traversed. Essentially, this rejection is based on the Examiner's belief that in order to claim the present invention, i.e., the coupling of known epitopes to a polyhydroxypolymer

carrier, it is necessary to characterize each individual epitope that could be used in such a method of creating an immunogen.

Again, the present invention is the provision of a novel way isolated epitopes are coupled to a polyhydroxypolymer carrier. The skilled artisan would readily appreciate that the present examples clearly show the general principle behind the present invention - the art recognizes that most effective immunogens MUST contain at least 1) a B-cell epitope or a CTL epitope and 2) at least a T-helper epitope, so these are simply the basic building blocks in most immunogens or vaccines. The present invention presents a novel way to combine these building blocks (through the N-termini coupling), and the present invention clearly shows that the inventors did indeed have access to the invention as used on other B-cell epitopes or CTL epitopes.

Again, if the present invention had related to a generally applicable adjuvant, Applicants doubt that the Examiner would hesitate to accept a claim of the format "An immunogenic composition comprising Adjuvant X in admixture with a peptide antigen" even in the event that the specification did not list all possible antigens in this world. The present invention is not very different from this - the single components of the immunogenic conjugates are all known in the prior art (polyhydroxypolymers are known, peptidic B-cell epitopes are known, CTL epitopes are known, and T-helper epitopes are known), but the specific way to combine these components is novel over the prior art. Applicants hold that any person skilled in the art would acknowledge that the present inventors could take a given B-cell epitope and a given T-helper epitope, couple their N-termini to a polyhydroxypolymer, and thereby provide an immunogen of the present invention.

Applicants assert that it can hardly be the meaning of the written description requirement to deny patentability of a generally applicable method or composition merely because the specification has not listed all possible species (in this case an almost infinite number) that would clearly be useful as components in the method or composition - especially not in a case where the inventive focus does not reside in the precise nature of these components. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claim 25 was also rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejection is respectfully traversed.

The Office Action stated that the limitation "a particle" does not have known metes and bounds. The claim has been amended herein to recite "an ISCOM particle" as described in the specification on page 34, line 27 to page 35, line 2. Accordingly, it is respectfully asserted that the rejection is now moot.

Consequently, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

IV. THE ART REJECTIONS ARE OVERCOME

Claims 1, 16, 18, 19 and 21 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by WO 00/20027 (Steinaa *et al.*). Also, claims 1, 2, 6, 11, 12, 14, 17, 20 and 21 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO 93/23076 (Cheronis). The rejections are traversed and will be addressed collectively.

Claim 1 has been amended to require that all peptides are coupled to the polyhydroxypolymer via their N-termini. It is respectfully asserted that this element of claim 1 is found nowhere in either of Steinaa *et al.* or Cheronis. Accordingly, the rejection cannot stand.

Consequently, reconsideration and withdrawal of the rejections under 35 U.S.C. §102 are respectfully requested.

CONCLUSION AND REQUEST FOR INTERVIEW

In view of the amendments and remarks herewith, which are fully responsive to the rejections, the application is in condition for allowance. Consideration and entry of this paper,

favorable reconsideration of the application and reconsideration and withdrawal of the objections to and rejections of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

If any issue remains as an impediment to allowance, an interview with the Examiner and the Examiner's SPE, is respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

Respectfully submitted,
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